**REMARKS**

Claims 78-101 are pending in the subject application. By this Amendment, applicants have canceled claim 101 and non-elected claims 78-86, 89-90, and 96-97 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims at a later date in a continuing application. Applicants have also amended claims 87, 91-95 and 98-100, and added new claims 102-109.

No new matter is introduced by the amendments to claim 87 which are supported in the specification at, *inter alia*, page 13, lines 28-30 and line 34 to page 14, line 8; page 14, lines 26-30; page 15, lines 11-13; page 17, lines 20-22; page 18, lines 18-19; page 19, lines 18-19 and line 36 to page 20, line 1; page 22, lines 33-35; and page 23, lines 4-5. The amendments to claims 91 are supported in the specification at, *inter alia*, page 17, lines 22-24. The amendments to claims 92-94 are supported in the specification at, *inter alia*, page 19, line 25 to page 20, line 1; and page 23, lines 3-7. Thus, these amendments do not raise any issue of new matter. Similarly, no new matter is introduced by the amendments to claims 95 and 98-100 which merely involve minor formatting changes and changes to their dependencies.

New claims 102-109 are fully supported in the specification as follows: Claim 102: page 13, lines 29-30; page 22, lines 6-10 and 33-35; Claim 103: page 22, line 37 to page 23, line 1; Claim 104: page 22, lines 36-37; Claim 105: page 14, lines 28-30; page 19, lines 6-10; Claim 106: page 13, line 34 to page 14, line 8, as amended herein; Claim 107: page 22, line 37 to page 23, line 1; Claim 108: page 22, lines 36-37; and Claim

109: page 14, lines 28-30; and page 19, lines 6-10. Thus, these new claims do not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 87-88, 91-95, 98-100 and 102-109 will be pending and under examination.

**Objections to the Specification**

On page 3 of the Office Action, the Examiner stated that the disclosure is objected to because of informalities which required appropriate corrective actions. Specifically, the Examiner stated that the bridging paragraph of pages 13-14 of the specification discusses a deposit but that it is unclear whether it is the antibodies or the hybridomas that produce the antibodies which applicants have deposited under the listed accession numbers.

In response, applicants have amended the specification as indicated hereinabove to indicate that murine hybridomas secreting MAbs PA8-PA12 and PA14 were deposited with the American Type Culture Collection (ATCC) under the indicated Accession Nos. A typographical error in the ATCC Accession No. for the PA14 hybridoma (HB-12610) has also been corrected. In support of these amendments, applicants attach hereto as **Exhibit A** two ATCC deposit receipts confirming the December 2, 1998 deposit of these hybridomas. Thus, these amendments to the specification do not raise any issue of new matter. Entry of these amendments into the application is therefore respectfully requested.

**Rejections under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 87-88, 91-95 and 98-101 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner stated that the invention appears to employ novel biological materials, specifically anti-CCR5 monoclonal antibodies designated ATCC Accession Nos. HB-12610, 12605, 12606, 12607, 12608 and 12609. The Examiner further stated that since the biological materials are specifically recited in the claims, and the components are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. The Examiner also stated that if they are not so obtainable or available, the requirements of 35.U.S.C. 112 may be satisfied by a deposit of biological materials.

The Examiner additionally stated that the specification does not disclose a repeatable process to obtain the biological materials and it is not apparent if the biological materials are readily available to the public. The Examiner also stated that it appears that applicants have deposited biological materials (citing page 13 of the specification), but that it is not clear what has been deposited. The Examiner further stated that there is no indication in the specification as to public availability.

The Examiner stated that if the deposit has been made under the Budapest Treaty, then an affidavit or declaration by

applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement.

In response, applicants affirm that hybridomas secreting the antibodies claimed in the subject invention were deposited on December 2, 1998, pursuant to the Budapest Treaty, with the Patent Culture Depository of the American Type Culture Collection (ATCC) under ATCC Accession Nos. HB-12605 (PA8), HB-12606 (PA9), HB-12607 (PA10), HB-12608 (PA11), HB-12609 (PA12) and HB-12610 (PA14). For the Examiner's convenience, applicants attach hereto as **Exhibit A** a copy of the December 29, 1998 Budapest Treaty Deposit Receipt and Viability Statement for the PA 10 hybridoma, and a copy of the December 30, 1998 Budapest Treaty Deposit Receipt and Viability Statement for the PA 8, 9, 11, 12 and 14 hybridomas.

Consistent with the requirements of C.F.R. 1.808, applicants' undersigned attorney states that the deposit of the antibodies was made under the terms of the Budapest Treaty, and that all restrictions on the availability to the public of the materials deposited under ATCC Nos. HB-12605, HB-12606, HB-12607, HB-12608, HB-12609 and HB-12610 will be irrevocably removed upon the granting of a patent from the subject application.

In view of the foregoing, applicants request that the Examiner withdraw this 35 U.S.C. §112, first paragraph rejection.

The Examiner also rejected claims 87-88, 91-95 and 98-101 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecule that encodes six CDR regions of the deposited antibodies, allegedly does not reasonably provide enablement for nucleic acid molecule that encodes less than six CDR regions of the deposited antibodies. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner stated that to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation (citing *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 [Fed. Cir. 1997]; *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 [Fed. Cir. 1993]; *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 [Fed. Cir. 1991]; *In re Fisher 427* F.2d 833, 839, 166 USPQ 18, 24 [CCPA 1970]). The Examiner also quoted from *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 [Fed. Cir. 1988]:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex *parte Forman* [230 USPQ 546, 547 (Bd. Pat. App. Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In addition, the Examiner asserted that it is well established

in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The Examiner also stated that the amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. The Examiner further stated that it is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce a protein having antigen-binding function, and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. The Examiner also stated even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc. Natl. Acad. Sci. U.S.A. [1982] 79: 1979) ("Rudikoff"). The Examiner further stated that Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

The Examiner stated that it is unlikely that a nucleic acid molecule that encodes less than the full complement of CDRs from the heavy and light chain variable regions of the antibodies that is produced from the deposited hybridomas, which is instantly claimed, have the required binding function and activity. The Examiner also stated that the specification provides no direction or guidance regarding how to produce a

nucleic acid molecule that encodes less than the full complement of CDRs from the heavy and light chain variable regions of the antibodies that is produced from the deposited hybridomas, nor does it teach one of ordinary skill in the art how to use such a nucleic acid molecule. The Examiner asserted that undue experimentation would be required to produce an invention commensurate with the scope of the claims based on the written disclosure alone.

The Examiner concluded that in view of the lack of guidance in the specification and in view of the statements above, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention. Further, the Examiner stated that a conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (citing *In re Wrigtht*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 [Fed. Cir. 1993]).

In response, applicants respectfully traverse the above rejections which applicants understand to apply to all the pending claims, as amended.

Applicants disagree with the Examiner's "expectation" that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce a protein having antigen-binding function, and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. In

this regard, applicants note that in some species, functional single-domain antibodies naturally lack light chains and contain only three CDR loops contributed by a heavy chain. For example, applicants respectfully direct the Examiner's attention to Desmyter et al. (2001) J. Biol. Chem. 276: 26285-26290 ("Desmyter"), attached hereto as **Exhibit B** (see abstract and first paragraph on page 26285). In particular, applicants note Desmyter's teaching that only the CDR3 region of a single-domain anti-carbonic anhydrase antibody interacts directly with the antigen (se page 26286, top of left col.).

Moreover, applicants note that even in an antibody consisting of heavy and light chains and comprising six CDRs, not all these CDRs necessarily bind to the target antigen. Thus, for example, Davies and Cohen (1996) Proc. Natl. Acad. Sci. U.S.A. 93: 7-12 (attached hereto as **Exhibit C**) teaches that in the interaction between influenza virus neuraminidase and the NC10 antibody, only four of the CDRs in NC10 make contact with the antigen (see page 8, sentence bridging central and right cols.). Similarly, in the interaction between HPr protein and the Jel42 antibody, CDR L2 does not contact the HPr (see page 9, first paragraph).

Further, applicants note that it has long been established that a peptide sequence as short as a single CDR can bind immunospecifically to an epitope and exhibit functional activity characteristic of the intact antibody. For example, applicants direct the Examiner's attention to the following papers, attached hereto as **Exhibit D**: Williams et al. (1989) Proc. Natl. Acad. Sci. U.S.A. 86: 5537-5541; Taub et al. (1989) J. Biol. Chem. 264: 259-265; Williams et al. (1991) J. Biol. Chem. 266: 5182-5190; and Bourgeois et al. (1998) J. Virol. 72:

807-810 ("Bourgeois"). Applicants note that these references (see, *inter alia*, the abstracts) reveal that methods for the identification of CDR sequences are well known in the art. For example, Bourgeois teaches that the sequences of the CDRs in a monoclonal antibody were deduced by alignment with other $V_H$ and $V_K$ sequences (see page 807, right col., second paragraph).

Given that CDRs can be readily identified in any given immunoglobulin molecule, applicants contend that one skilled in the art can easily produce, without undue experimentation, a nucleic acid sequence coding for a polypeptide comprising one or more CDRs, using well known recombinant DNA techniques such as PCR amplification. Applicants respectfully submit, therefore, that the Examiner's statement that the specification provides no direction or guidance regarding how to produce a nucleic acid molecule that encodes less than the full complement of CDRs from the heavy and light chain variable regions of the antibodies is without merit. Applicants maintain that, in fact, methods for producing a nucleic acid molecule that encodes a polypeptide comprising less than the full complement of CDRs are so well known in the art that their detailed description in the specification would be superfluous.

Applicants emphasize that not only can single CDR sequences bind to a target epitope but they can also exhibit the biological activity of the intact antibody. The Bourgeois study provides a particularly appropriate example in the context of the present application since it discloses the use of a CDR sequence capable of binding to, and inhibiting infection by, a human virus. This study teaches that a peptide sequence, corresponding to a single CDR of a neutralizing antibody against respiratory synctial virus (RSV), inhibits RSV

infectivity both *in vitro* and *in vivo* with the same subgroup neutralizing specificity as the antibody (see abstract; page 808, second paragraph; and page 809, final paragraph). Applicants maintain, therefore, that it is well known in the art how to use a CDR for binding to an epitope and eliciting the biological activity of the intact antibody.

Applicants note the Examiner's reliance on Rudikoff to suggest that even minor changes in the amino acid sequences of the CDRs may dramatically affect antigen binding. The Examiner appears to conclude from Rudikoff that *any* change in the structure of the CDRs, including the use of an antibody portion comprising less than the full complement of six CDRs, is detrimental to antibody binding.

In response, applicants respectfully disagree with the Examiner's apparent interpretation of Rudikoff.

Applicants contend that the fact that a particular mutation in a CDR causes a significant effect on antigen binding in no way implies that *any* change in amino acid sequence of the CDR will have such an effect. Several studies have indicated that, on the contrary, many changes in the amino acid sequence within a CDR have little effect on the antigen-binding function of a CDR. For example, applicants direct the Examiner's attention to Parhami-Seren et al. (2001) J. Immunol. 167: 5129-5135, attached hereto as **Exhibit E**. This reference (see abstract) demonstrates that whereas two particular mutations in HCDR2 of an antibody, 36-71, resulted in significant loss of binding, all other mutations in HCDR2 had minimal effect on antibody affinity.

In light of the arguments set forth above, applicants maintain that, based on the disclosures in the subject specification, one of ordinary skill in the art could, without undue experimentation, make and use an isolated nucleic acid encoding a polypeptide, the amino acid sequence of which is identical to the sequence of a CDR present in PA14 or one of the other monoclonal antibodies recited in the claims. Thus, applicants maintain that the claimed invention is fully enabled by the specification as filed.

**Double Patenting**

The Examiner provisionally rejected claims 87-88, 91-95 and 98-101 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 4-13 of copending Application No. 10/081,128. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the cited application are directed to nucleic acids that encode anti-CCR5 monoclonal antibodies and CDR regions of such antibodies. The Examiner also stated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response, and without conceding the correctness of the Examiner's position, applicants note that U.S. serial No. 10/081,128, filed February 22, 2002, has been abandoned, thereby rendering this rejection moot.

**Conclusion**

In view of the remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the claim rejections set forth in the April 2, 2004 Office Action, and earnestly solicit allowance of all claims pending in the subject application.